2. SCIENTIFIC ABSTRACT

Early detection by routine screening of pre-neoplastic lesions has made a serious impact on cervical cancer mortality in the Western hemisphere. However, cervical cancer is still the second leading cause of cancer death in women worldwide and a significant source of cancer death for poor and/or uninsured women in the US. About 50% of cervical cancer is the result of transformation by Human Papilloma Virus (HPV) strain 16 and has an obligatory association with the HPV transforming proteins E6 and E7.

Listeria monocytogenes (Lm) has been shown to be an unusually potent stimulator of cellular immune responses to secreted antigens, including recombinant antigens that the bacterium has been engineered to express and secrete. Lm-LLO-E7 is a novel recombinant therapeutic cancer vaccine that is comprised of live, attenuated *L. monocytogenes* bacteria, which are genetically modified to express HPV type 16 E7 tumor antigen, linked to listeriolysin O (LLO) protein. When the engineered *Listeria* (Lm-LLO-E7) are introduced to the body, they are engulfed by antigen presenting cells in the immune system. The bacteria enter the cytoplasm of the cells and produce the LLO-E7 protein. This protein is then degraded and presented on the surface of the cells thereby producing an immune response. Specifically, antigen presentation signals immune effector cells, especially cytotoxic T-lymphocytes, to recognize and kill cells presenting this antigen. Additionally, some of the LLO-E7 antigen produced by the *Listeria* is processed by the immune system to stimulate a lymphoproliferative response. In mouse tumor models Lm-LLO-E7 has been shown to increase survival and induce regression of tumors immortalized by HPV and transformed RAS.

The proposed clinical protocol is an intravenous dose-escalation study to investigate the safety and immunogenicity of Lm-LLO-E7 in female patients with a progressive, recurrent or advanced squamous cell carcinoma of the cervix that is metastatic or unresectable and for which standard curative or palliative measure do not exist or are no longer effective. Patients will receive Lm-LLO-E7 administered intravenously every 21 days for a total of three treatments. The primary objective of this study is to establish the safety and tolerability of vaccination with Lm-LLO-E7. The secondary objective of this study is to determine the type of immunity induced against E7 delivered by the vector and its relationship to the number of organisms delivered in the vaccine.

Because this agent has not been used in human trials to date, this preliminary Phase 1 study will be conducted in patients with advanced disease for whom no standard effective curative or palliative therapy is available. A major consideration is the safety of using a live bacterium in potentially immunocompromised advanced cancer patients who may have received heavy pretreatment with radiation and chemotherapy. Clinical listeriosis is treatable in both immune competent and immune compromised individuals with a wide range of antibiotics. In addition, the pathogenicity of the mutant *L. monocytogenes* used for vaccination is significantly attenuated. In murine studies, the LD_{50} of Lm-LLO-E7 is roughly 3 logs higher than wild type *L. monocytogenes* responsible for clinical infections.